CHAPTER 25
Thyroid and Its Disorders

KEY TEACHING POINTS

- The normal thyroid has a constant relationship to the two most prominent landmarks of the neck, the laryngeal prominence (of the thyroid cartilage) and the cricoid cartilage. The best definition of goiter is enlarged thyroid lobes (e.g., each larger than the distal phalanx of the patient's thumb), apparent by both inspection and palpation (without extending the neck).
- 75% to 90% of patients with *substernal* goiters also have *cervical* goiters. One-third of patients with substernal goiters have a displaced trachea; some develop congestion of the face when they elevate their arms (Pemberton sign).
- In patients with thyroid nodules or goiters, the presence of cervical adenopathy, vocal cord paralysis, or fixation to adjacent tissues greatly increases probability of carcinoma.
- In patients with suspected thyroid disease, the findings that increase probability of hypothyroidism the most are hypothyroid speech; cool, dry, and coarse skin; bradycardia; and delayed ankle reflexes.
- In patients with suspected thyroid disease, the findings that increase probability of hyperthyroidism the most are eyelid retraction, eyelid lag, fine finger tremor, moist and warm skin, and tachycardia.

GOITER

I. INTRODUCTION

In industrialized areas of the world, goiter (i.e., enlarged thyroid) occurs in up to 10% of women and 2% of men, the usual causes being multinodular goiter, Hashimoto thyroiditis, or Graves disease (the most common cause worldwide is endemic goiter, largely from inadequate iodine intake).[1] Approximately 80% of patients with goiter are clinically euthyroid; 10% are hypothyroid, and 10% are hyperthyroid. Most patients are asymptomatic or present for evaluation of a neck mass. A few patients, especially those with substernal goiters, present with dyspnea, stridor, hoarseness, or dysphagia (see the section on Substernal Goiters later).

Endemic goiter has been described for millennia, although it is unclear whether early clinicians distinguished goiter from other causes of neck swelling, such as tuberculous lymphadenitis. The first person to clearly differentiate cystic goiter from cervical lymphadenopathy was Celsus, the Roman physician writing in AD 30.[2]

II. TECHNIQUE

A. NORMAL THYROID[3]

The important landmarks for locating the thyroid gland are the V at the top of the thyroid cartilage (the *laryngeal prominence* of the thyroid cartilage) and the cricoid cartilage (Fig. 25.1). These two structures, which are usually 3 cm apart, are the most conspicuous structures in the midline of the neck. The isthmus of the normal thyroid lies just below the cricoid cartilage and is usually 1.5 cm wide, covering the second through fourth tracheal rings. Each lateral lobe of the thyroid is 4 to 5 cm long and hugs the trachea tightly, extending from the middle of the thyroid cartilage down to the fifth or sixth tracheal ring. A pyramidal lobe is found in up to 50% of anatomic dissections, usually on the left side, and is palpable in 10% of nontoxic goiters but seldom in normal-sized glands.

The thyroid has a constant relationship with the laryngeal prominence (which is approximately 4 cm above the thyroid isthmus) and the cricoid cartilage (which is just above the isthmus), but the position of these structures in the neck (and thus of the thyroid in the neck) varies considerably among patients (see Fig. 25.1).[4] If the laryngeal prominence and suprasternal notch of the manubrium are far apart (separated by more than 10 cm), the patient may have a conspicuous *high-lying thyroid*, which resembles a goiter even though it is normal sized (see the section on Pseudogoiter later). If the laryngeal prominence is close to the suprasternal notch (separated by less than 5 cm), the patient has a *low-lying thyroid*, which often is concealed behind the sternocleidomastoid muscles and clavicles, making complete palpation of the gland impossible.[4,5] Low-lying thyroids are more common in elderly patients.

In areas of the world with iodine-replete diets, the normal thyroid is less than 20 mL in volume.[6]

B. EXAMINATION FOR GOITER

1. INSPECTION

Two maneuvers make the thyroid more conspicuous: (1) extending the patient's neck, which lifts the trachea (and thyroid) approximately 3 cm away from the suprasternal notch and stretches the skin against the thyroid and (2) inspecting the

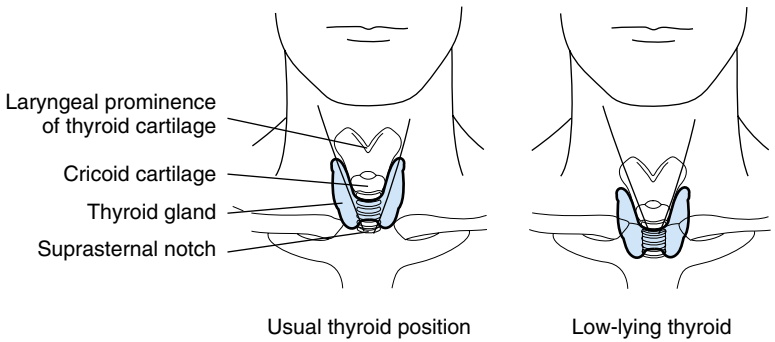

FIG. 25.1 THE NORMAL THYROID. The thyroid gland has a constant relationship with the two most prominent landmarks of the middle of the neck—the laryngeal prominence of the thyroid cartilage and the cricoid cartilage. On the left is the usual position of the thyroid gland. On the right is a *low-lying thyroid*, most of which is hidden behind the clavicles and sternum, inaccessible to palpation.

patient's neck from the side. In patients with normal- or high-lying thyroids, the line between the cricoid prominence and suprasternal notch, when viewed from the side, should be straight. Anterior bowing of this line suggests a goiter (Fig. 25.2).[7]

2. PALPATION

Palpation of the thyroid may proceed from the patient's front or back, whichever is most comfortable and effective for the clinician, because studies fail to show either method to be superior.[8] The patient's neck should be slightly flexed (to relax the sternocleidomastoid and sternohyoid muscles), and a firm technique should be used. The following features should be noted: thyroid size, consistency (i.e., soft, firm, or hard; a "soft" thyroid has the consistency of the surrounding tissue in the neck), texture (diffuse or nodular), tenderness, tracheal deviation (a clue to asymmetric goiter), and lymphadenopathy.

3. OBSERVING THE PATIENT SWALLOW[9]

Because the thyroid and trachea are firmly attached by ligaments and must move together, observation as the patient swallows helps to distinguish thyroid tissue from other neck structures. During a normal swallow, both the thyroid and trachea make an initial upward movement of 1.5 to 3.5 cm; the larger the oral bolus, the greater the movement. The thyroid and trachea then hesitate 0.2 to 0.7 second before returning to their original position.

Therefore a neck mass is probably not in the thyroid if one of the following is detected: (1) the mass is immobile during a swallow or moves less than the thyroid cartilage; (2) the mass does not hesitate before descending to its original position;

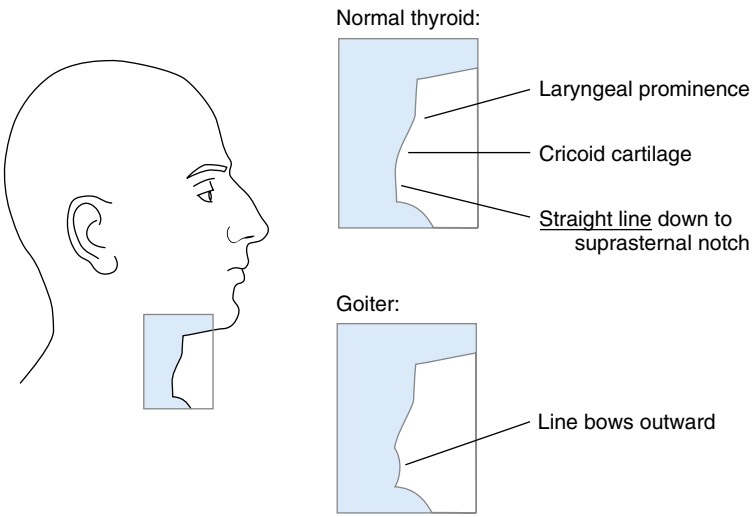

FIG. 25.2 NECK CONTOUR AND GOITER. The shaded profile of the neck (*left*) is enlarged on the right, to contrast the normal thyroid contour with that of a goiter. Below the cricoid cartilage, the contour of the normal neck in the midline (*top right*) is a straight line downward to the suprasternal notch. In patients with goiter, this line bows outward (*bottom right*) because of enlargement of the thyroid isthmus. This line is visible only in patients with normal-lying and high-lying thyroids, not low-lying thyroids (see Fig. 25.1).

or (3) the mass returns to its original position before complete descent of the thyroid cartilage.

III. THE FINDINGS

A. CERVICAL GOITER

Common definitions of goiter include the following: (1) **Rule of thumb.** This states that a lateral lobe is enlarged if it is larger than the distal phalanx of the patient's thumb. (2) **Estimates of thyroid volume by palpation**. For example, a thyroid whose lateral lobes each measure 3 cm wide, 2 cm deep, and 5 cm long would have an estimated volume of 60 mL (i.e., $2 \times 3 \times 2 \times 5 = 60$). Any estimate more than 20 mL is classified as a goiter (i.e., each lateral lobe is normally less than 10 mL). (3) **Epidemiologic definitions of goiter.** These definitions are designed for clinicians who survey large numbers of persons rapidly in areas of endemic goiter (some clinicians examine 150 to 200 patients per hour). The revised World Health Organization definition has three grades: grade 0—no palpable or visible goiter, grade 1—goiter that is palpable *but not visible* with the head in the normal position, and grade 2—a goiter that is clearly visible when the neck is in a normal position.[10]

B. SUBSTERNAL AND RETROCLAVICULAR GOITERS

Large goiters may extend from the neck to the superior mediastinum, passing through the inflexible thoracic inlet (i.e., the bony ring formed by the upper sternum, first ribs, and first thoracic vertebral body). At the thoracic inlet, such goiters may compress the trachea, esophagus, or neck veins and thus produce dyspnea, dysphagia, facial plethora, cough, and hoarseness. Sometimes, when these patients flex or elevate the arms, the thoracic inlet is pulled up into the cervical goiter, just as if the thyroid were a cork and the thoracic inlet were the neck of a bottle. This causes the characteristic **Pemberton sign**, which is congestion of the face, cyanosis, and eventual distress induced by arm elevation (Fig. 25.3).[11-13] The exact frequency of Pemberton sign is unknown. In two small series of patients with substernal goiter, it was present in every patient,[14,15] whereas other large series did not make mention of the sign at all.[16,17]

In patients with substernal goiters, associated findings include cervical goiter (i.e., palpable goiter above the thoracic inlet, 75% to 90% of patients), tracheal deviation (33% by palpation, 75% by chest radiograph), distended neck veins (5% to 20%), and stridor (7% to 16%).[16-18]

C. THYROGLOSSAL CYST[19]

Thyroglossal cysts are cystic swellings of the thyroglossal duct, an epithelium-lined remnant marking the embryologic descent of thyroid tissue from the base of the tongue to its final location anterior to the larynx. Thyroglossal cysts present at any age, appearing as tense, nontender, mobile, nonlobulated round tumors, usually at the level of the hyoid bone or just below it (the hyoid bone is *above* the thyroid cartilage). Pain and tenderness may follow infection or acute hemorrhage into the capsule. The cysts are in the midline of the neck, unless they are so low they lie to one side of the thyroid cartilage. Despite their cystic structure, they do not usually transilluminate. If the cyst remains attached to the base of the tongue or hyoid bone, a characteristic physical sign of thyroglossal cysts is upward movement when the patient protrudes the tongue, just as if the two structures were connected by a string. Thyroglossal cysts account for three-quarters of congenital neck masses, the

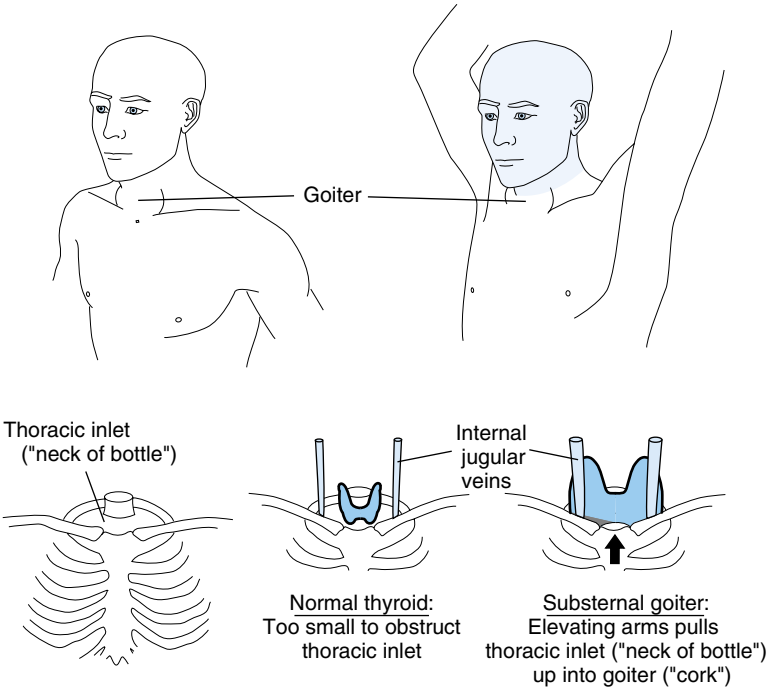

FIG. 25.3 PEMBERTON SIGN. If a patient with retrosternal goiter elevates his arms (*top row*), dramatic facial congestion may occur (i.e., positive Pemberton sign). This occurs because the thoracic inlet ("neck of bottle," *bottom left*) is an inflexible bony ring formed by the first thoracic vertebra, first ribs, and upper sternum (its outline is about the same size and shape as the patient's kidney). A normal-sized thyroid (*bottom middle*) is too small to obstruct the thoracic inlet. In contrast, a goiter of sufficient size (*bottom right*) may obstruct the thoracic inlet, especially if the goiter extends below the sternum and the patient elevates his arms (which pulls the thoracic inlet, or "neck of bottle" up into the goiter, or "cork," *arrow*).

other one-quarter being branchial cleft cysts, which are located more laterally, usually anterior to the sternocleidomastoid muscle at the level of the hyoid bone.[20,21]

D. PSEUDOGOITER

Pseudogoiter refers to thyroid glands that appear enlarged even though they are normal sized. There are three causes: (1) **High-lying thyroid gland**, which, although normal sized, lies so high in the neck it is unusually conspicuous after neck extension. In these patients the laryngeal prominence is 10 cm or more above the suprasternal notch and both thyroid lobes are smaller than the distal phalanx of the patient's thumb. In one study, high-lying but normal-sized thyroids accounted for 8% of suspected goiters referred to an endocrinology service.[4] (2) Other cervical masses, such as adipose tissue, cervical lymphadenopathy, branchial cleft cysts, and pharyngeal diverticula (see Chapter 27). Observation during swallowing helps to identify these lesions. (3) **Modigliani syndrome**, which describes a normal-sized thyroid lying in front of an exaggerated cervical spine lordosis,[22] named after the painter Amedeo Modigliani, whose portraits had subjects with long, curved necks.

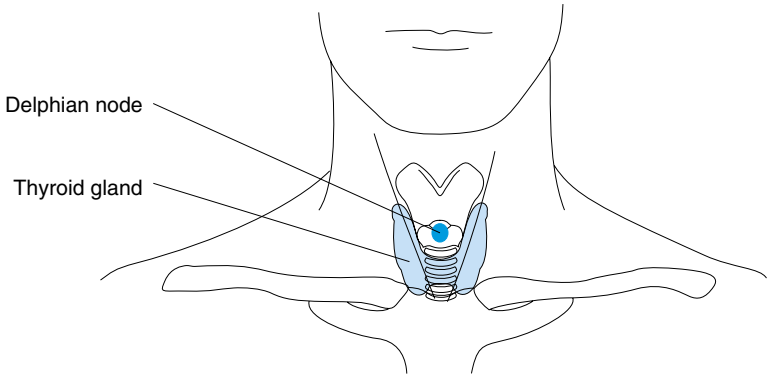

FIG. 25.4 THE DELPHIAN NODE. The Delphian node lies in the midline of the neck, just above the thyroid isthmus and in front of the cricothyroid ligament, where it can easily be palpated against the unyielding cricoid cartilage.

E. THE DELPHIAN NODE

The Delphian node, a lymph node that drains the thyroid gland and larynx, lies directly anterior to the cricothyroid ligament (just cephalad to the thyroid isthmus, Fig. 25.4). When enlarged, the node is readily palpable because of its superficial location in front of the unyielding trachea. The node is called *Delphian* because it is the first one exposed during surgery, and its appearance often foretells what the surgeon will find in the thyroid (e.g., carcinoma), just as the oracle at Delphi foretold the future.* The Delphian node enlarges in some patients with thyroid cancer, Hashimoto thyroiditis, and laryngeal cancer. Its involvement in both laryngeal and thyroid cancer is associated with a worse prognosis.[24-26]

IV. CLINICAL SIGNIFICANCE

A. DETECTING GOITER

The findings listed in EBM Box 25.1 are categorized into three levels: (1) no goiter by palpation or inspection (including inspection of the extended neck); (2) goiter by palpation, but the gland is not conspicuous until the patient's neck is extended; and (3) goiter by palpation and inspection with the neck in the normal position. The first finding, absence of goiter by inspection and palpation, decreases the probability of enlarged thyroid modestly (likelihood ratio [LR] = 0.4; see EBM Box 25.1). Although up to half of patients with enlarged glands by ultrasonography have this finding, these goiters are presumably small. The intermediate finding (i.e., goiter by palpation but visible only after neck extension) fails to distinguish goiter from normal-sized glands (LR not significant), suggesting that subtle enlargement by palpation without a visible goiter (in the normal neck position) is an unreliable sign of goiter. A gland that is both enlarged by palpation and visible when

*The word *Delphian* was originally suggested by Raymond Randall, a fourth-year medical student attending the thyroid clinic at Massachusetts General Hospital.[23]

EBM BOX 25.1
*Goiter**

Finding (Reference)	*Sensitivity (%)*	*Specificity (%)*	*Likelihood Ratio† if Finding Is Present*
No goiter by palpation or inspection[7,27-31]	5-57	0-40	0.4
Goiter by palpation, visible only after neck extension[27]	13	—	NS
Goiter by palpation and inspection with neck in normal position[27-29,31]	43-82	88-100	**26.3**

*Diagnostic standard: for *goiter,* ultrasound volume greater than 20 mL,[27-29,31] ultrasound volume greater than 18 mL (women) or greater than 25 mL (men),[30] or surgical weight greater than 23 g.[7]
†Likelihood ratio (LR) if finding present = positive LR; LR if finding absent = negative LR.
NS, Not significant.
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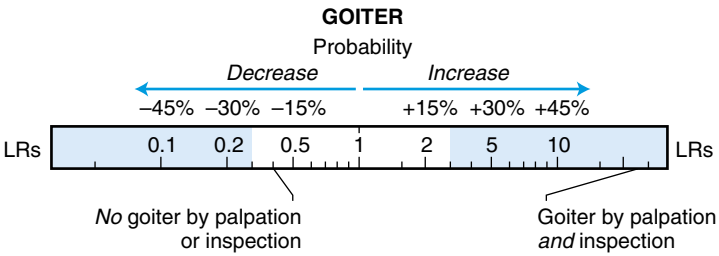

the patient's neck is in the normal position greatly increases the probability of an enlarged thyroid (LR = 26.3).

B. ETIOLOGY OF GOITER

In clinically euthyroid patients with goiter, the most common causes are multinodular goiter or Hashimoto thyroiditis. In hypothyroid patients it is Hashimoto thyroiditis, and in hyperthyroid patients it is Graves disease or multinodular goiter. The associated finding of ophthalmopathy (tearing, diplopia, proptosis) or dermopathy (pretibial myxedema) indicates Graves disease (see the section on Graves Ophthalmopathy).

Although thyroid cancer can also cause a goiter, cancer usually presents instead as a thyroid nodule (see the section on Thyroid Nodule). Three findings increase the probability that a goiter contains carcinoma: cervical adenopathy (LR = 15.4; EBM Box 25.2), vocal cord paralysis (LR = 11.3), and fixation of the goiter to surrounding tissues (LR = 10.5).

Silent and postpartum lymphocytic thyroiditis may also produce a goiter, but it is rarely prominent and the clinician's attention is instead directed toward the findings of hyperthyroidism or hypothyroidism.[36] The finding of a painful or tender

EBM BOX 25.2

*Goiter and Thyroid Nodules—Findings Predicting Carcinoma**

Finding (Reference)†	*Sensitivity (%)*	*Specificity (%)*	Likelihood Ratio‡ if Finding Is	
			Present	*Absent*
Goiter				
Cervical adenopathy[32]	45	97	**15.4**	0.6
Vocal cord paralysis[17,32]	24-44	94-99	**11.3**	0.7
Fixation to surrounding tissues[32]	60	94	**10.5**	0.4
Goiter nodular (vs. diffuse)[32]	78	49	1.5	0.5
Pyramidal lobe present[32]	2	90	NS	NS
Thyroid Nodule				
Vocal cord paralysis[33,34]	5-14	99-100	**17.9**	NS
Fixation to surrounding tissues[33,35]	13-37	95-98	**7.8**	NS
Cervical adenopathy[33,34]	24-31	96-97	**7.2**	0.8
Diameter ≥4 cm[35]	66	66	1.9	0.5
Very firm nodule[33]	3	99	NS	NS

*Diagnostic standard: for *carcinoma,* pathologic examination of tissue.[32-35]
†Definition of findings: for vocal cord paralysis, visualization of vocal cords[32-34] or symptomatic dysphonia.[17]
‡Likelihood ratio (LR) if finding present = positive LR; LR if finding absent = negative LR.
NS, Not significant.
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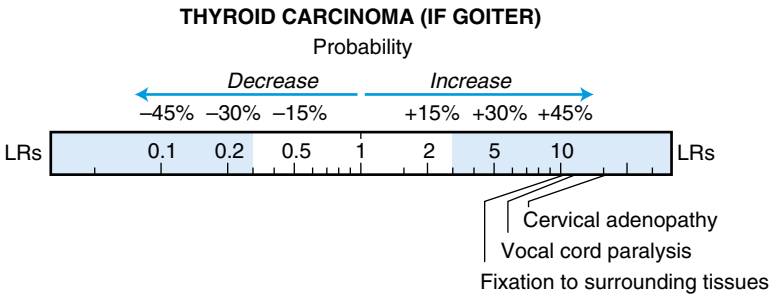

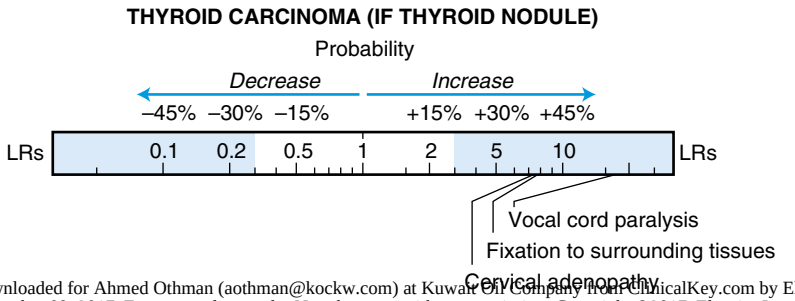

thyroid gland, sometimes mimicking pharyngitis, suggests subacute thyroiditis[37] or hemorrhage into a cyst or nodule (although most thyroid hemorrhage is painless).[38] In subacute thyroiditis, the thyroid is modestly enlarged, usually 1.5 to 3 times the normal size.

THYROID NODULES

I. INTRODUCTION[39]

Palpable thyroid nodules occur in approximately 5% of women and 1% of men, most of whom are clinically euthyroid. Although thyroid nodules raise concerns about thyroid cancer, more than 95% of nodules reflect benign disorders, such as colloid cysts, adenomas, or dominant nodules of a multinodular gland.

II. OCCULT NODULES

Because thyroid nodules are palpable in only 1% to 5% of persons yet are discovered in up to 50% of patients during ultrasound or autopsy surveys,[40] it is obvious that most thyroid nodules are occult (i.e., detectable by clinical imaging but not by palpation). Furthermore, when the clinician feels a single palpable nodule in the patient's thyroid gland, ultrasonography reveals multiple nodules half the time.[41] Occult nodules are not palpable either because the patient's neck is too short or thick,[42] the nodules are buried in the posterior parts of the gland,[43] or the nodules are too small (i.e., the mean diameter of a palpable nodule is 3 cm; palpation fails to detect 50% of nodules less than 2 cm in diameter and more than 90% of nodules less than 1 cm in diameter).[42]

III. CLINICAL SIGNIFICANCE

The most important diagnostic test for thyroid nodules is fine needle aspiration. Nonetheless, a few signs, if present, increase the probability of carcinoma in thyroid nodules (see EBM Box 25.2): vocal cord paralysis (LR = 17.9), fixation of the nodule to surrounding tissues (LR = 7.8), and cervical adenopathy (LR = 7.2). However, all of these findings are insensitive, with fewer than one of three patients with carcinomatous nodules having any of these findings.

HYPOTHYROIDISM (MYXEDEMA)

I. INTRODUCTION

Hypothyroidism is a clinical syndrome that results from diminished levels of thyroid hormone, which reduces the patient's metabolic rate, slows neuromuscular reactions, and causes mucopolysaccharides to accumulate in skin and other tissues throughout the body. In areas of the industrialized world with iodine-replete diets, hypothyroidism affects 9% of women and 1% of men.[1] The usual cause is disease in the thyroid gland itself (primary hypothyroidism), most often from Hashimoto thyroiditis (60% to 70% of cases) or previous radioiodine treatment for Graves disease (20% to 30% of cases).[1]

The diagnosis of hypothyroidism relies on laboratory tests, which have been available for more than 100 years.[†] Nonetheless, bedside diagnosis is still essential for two reasons: (1) examination estimates the likelihood of thyroid disease, which then can be used to identify subgroups of patients with high or low probability of abnormal thyroid function, thus increasing the yield of laboratory testing; and (2) examination is essential when diagnosing subclinical hypothyroidism or sick euthyroid syndrome, conditions that by definition describe patients with abnormal laboratory tests but without bedside findings of thyroid disease.

All of the classic bedside findings of hypothyroidism—puffy skin, slow reflexes, thick speech, and sluggish thinking—were first described by William Gull and William Ord in the 1870s.[45,46]

II. FINDINGS AND THEIR PATHOGENESIS

A. SKIN AND SOFT TISSUE[47,48]

The nonpitting puffiness of hypothyroidism results from dermal accumulation of mucopolysaccharides (mostly hyaluronic acid and chondroitin sulfate), which freely bind water. These changes cause a "jelly-like swelling (and) overgrowth of mucus-yielding cement," which led Ord to coin the term "myxedema" in 1877.[46] Even after effective thyroid replacement, these changes may persist for months.

Some myxedematous patients also have a yellow tint to their skin, which occurs because of hypercarotinemia from diminished conversion of carotenoids to retinol. The apparent coolness of the skin is attributed to diminished dermal blood flow, and dryness results in part from decreased sebum production. The loss of hair from the lateral eyebrows occurs in some hypothyroid patients but is one of the least specific signs (see later).

B. THE ACHILLES REFLEX

The ankle jerk has been investigated more extensively than any other physical finding of thyroid disease. By the 1970s at least nine different instruments had been designed to precisely measure the duration of reflex to the nearest millisecond. Both the contraction and relaxation phase of the ankle jerk are prolonged in hypothyroidism, although prolonged relaxation seems most prominent to the human eye (and on many of the tracings of the reflex). In one study the mean half-relaxation time (i.e., the time from the hammer tap to the moment the Achilles tendon has returned half-way to its original position) for hypothyroid patients was 460 ms (standard deviation [SD]: 40 ms), compared with 310 ms (SD: 30 ms) for euthyroid patients.[49] Experiments in hypothyroid rats suggest that the prolongation results from diminished calcium transport by the sarcoplasmic reticulum and subsequent slowing of the interaction between actin and myosin.[50]

When testing for hypothyroidism, clinicians usually elicit the ankle jerk by tapping on the Achilles tendon with the patient kneeling on a chair.[‡] The force of

[†] The first thyroid test was the basal metabolic rate (BMR) (i.e., oxygen consumption), introduced in the 1890s; radioactive iodine uptake appeared in the 1940s; serum protein-bound iodide (PBI) in the 1950s; serum total thyroxine (T4) in the 1960s; and sensitive assays for thyroid-stimulating hormone (TSH) in the 1980s.[44]

[‡] Other muscle stretch reflexes may also be delayed in hypothyroidism, as illustrated in an online video of a delayed biceps reflex.[51]

the tap does not affect the duration of the reflex, although slightly more force is necessary in hypothyroid patients to generate a reflex than in hyperthyroid patients.

C. HYPOTHYROID SPEECH

Hypothyroid speech, seen in approximately one-third of patients with hypothyroidism, has a slow rate and rhythm and is characteristically deep, low-pitched, and hyponasal (i.e., as if the patient has a cold).[52] Some patients even slur their words slightly, leading one clinician to describe the hypothyroid voice as "a bad gramophone record of a drowsy, slightly intoxicated person with a bad cold and a plum in the mouth"[53] Biopsies of vocal cords have revealed deposition of mucinous material.

D. OBESITY

Obesity is no more common in hypothyroid patients than euthyroid patients.[54]

III. CLINICAL SIGNIFICANCE

EBM Box 25.3 summarizes the diagnostic accuracy of physical signs associated with hypothyroidism, as applied to more than 1500 patients with suspected thyroid disease. The **Billewicz scoring scheme**, which combines symptoms and signs, is fully described in Table 25.1.

In patients with suspected thyroid disease, the findings increasing the probability of hypothyroidism the most are hypothyroid speech (LR = 5.4; see EBM Box 25.3), cool *and* dry skin (LR = 4.7), slow pulse rate (LR = 4.2), coarse skin (LR = 3.4), and delayed ankle reflexes (LR = 3.4).[§] Hair loss of the eyebrows is one of the least compelling diagnostic signs (LR = 1.9), and the finding of *isolated* coolness or dryness of the palms is unhelpful (LR not significant). No individual finding, when present or absent, significantly decreases the probability of hypothyroidism (i.e., no LR has a value less than 0.6).

A Billewicz score of +30 points or higher greatly increases the probability of hypothyroidism (LR = 18.8), whereas a score less than −15 points decreases the probability of hypothyroidism (LR = 0.1). The Billewicz score may perform less well in elderly patients, who, as a rule, have fewer findings than younger patients.[62]

HYPERTHYROIDISM

I. INTRODUCTION

Hyperthyroidism is a clinical syndrome due to increased production or release of thyroid hormone, which elevates the metabolic rate and causes characteristic findings of the skin, thyroid, eyes, and neuromuscular system. The most common causes of hyperthyroidism are Graves disease (60% to 90% of cases), toxic nodular goiter, thyroiditis (subacute, silent, or postpartum), and iatrogenic overtreatment with thyroid replacement.[63] Hyperthyroidism affects women (4% prevalence) more than men (0.2% prevalence).

[§] Precise measurements of the ankle jerk using special instruments discriminate well between patients with and without hypothyroidism: the finding of a half-relaxation time greater than 370 to 380 ms detects hypothyroidism with a sensitivity of 91% to 99%, specificity of 94% to 97%, positive LR = 18.7, and negative LR = 0.1.[49,55,61]

EBM BOX 25.3
*Hypothyroidism**

Finding (Reference)†	*Sensitivity (%)*	*Specificity (%)*	Likelihood Ratio‡ if Finding Is	
			Present	*Absent*
Skin				
Cool and dry skin[55]	16	97	**4.7**	0.9
Coarse skin[56,57]	29-61	74-95	**3.4**	0.7
Cold palms[56]	37	77	NS	NS
Dry palms[56]	42	73	NS	NS
Periorbital puffiness[56,57]	53-91	21-81	NS	0.6
Puffiness of wrists[56]	39	86	2.9	0.7
Hair loss of eyebrows[56]	29	85	1.9	NS
Pretibial edema[57]	78	31	NS	NS
Speech				
Hypothyroid speech[56]	37	93	**5.4**	0.7
Pulse				
Slow pulse rate[55,57,58]	29-43	89-98	**4.2**	0.7
Thyroid				
Enlarged thyroid[55]	46	84	2.8	0.6
Neurologic				
Delayed ankle reflexes[57]	48	86	**3.4**	0.6
Slow movements[57]	87	13	NS	NS
Billewicz Score[59,60]				
Less than −15 points	3-4	28-68	**0.1**	—
−15 to +29 points	35-39	—	NS	—
+30 points or more	57-61	90-99	**18.8**	—

*Diagnostic standard: for *hypothyroidism*, low free thyroxine (T4) level and high thyroid-stimulating hormone (TSH),[57,58,60] or low protein-bound iodide (PBI) level.[55,56,59] The PBI level and total T4 level correlate closely, except in patients with thyroiditis or those who ingest exogenous iodides (e.g., radiocontrast dye, cough suppressants), diagnoses in which the PBI level may be falsely high. However, these diagnoses were largely excluded from the studies reviewed here.
†Definition of findings: for slow pulse rate, less than 60 beats/min[57,58] or less than 70 beats/min,[55] for delayed ankle reflexes, assessment of contraction and relaxation of calf muscle by naked eye,[57] for slow movements, patients required more than 1 min to fold a 2-m-long bed sheet.[57]
‡Likelihood ratio (LR) if finding present = positive LR; LR if finding absent = negative LR.
NS, Not significant.
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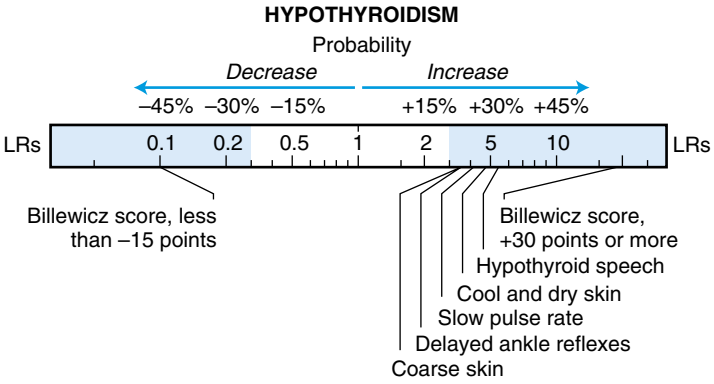

TABLE 25.1 Billewicz Diagnostic Index for Hypothyroidism

Finding*	POINTS SCORED IF FINDING IS Present	Absent
SYMPTOMS		
Diminished sweating	+6	−2
Dry skin	+3	−6
Cold intolerance	+4	−5
Weight increase	+1	−1
Constipation	+2	−1
Hoarseness	+5	−6
Paresthesia	+5	−4
Deafness	+2	0
PHYSICAL SIGNS		
Slow movements	+11	−3
Coarse skin	+7	−7
Cold skin	+3	−2
Periorbital puffiness	+4	−6
Pulse rate <75/min	+4	−4
Slow ankle jerk	+15	−6

**Definition of findings:* For *weight increase,* recorded increase in weight or tightness in clothing; for *slow movements*, observations while patient removing and replacing a buttoned garment; for *coarse skin,* roughness and thickening of skin of hands, forearms, and elbows; for *slow ankle jerk*, reflex appears slow with patient kneeling on a chair, grasping its back.
Based upon reference 59.

Three clinicians—Caleb Parry, Robert Graves, and Adolf von Basedow—all writing between 1825 and 1840, independently described the classic physical signs associated with thyrotoxicosis. All three were especially impressed with the triad of goiter, prominent eyes, and forceful tachycardia.[64]

II. FINDINGS AND THEIR PATHOGENESIS

A. THE THYROID

A goiter is present in 70% to 93% of patients with hyperthyroidism.[65-67] The goiter is diffuse and symmetric in patients with Graves disease and thyroiditis, but nodular in those with toxic nodular goiter.[67]

A thyroid bruit is a common feature of Graves disease (73% of patients in one study).[68] Nonetheless, the finding also was noted in 30% of elderly patients with toxic nodular goiter,[69] suggesting that the finding is not as specific for Graves disease as is classically taught. Bruits often radiate far from their source, and perhaps the "thyroid bruit" in the elderly with toxic nodular goiter is actually a carotid bruit made prominent by the increased cardiac output of hyperthyroidism.**

B. EYE FINDINGS

Three distinct eye findings are associated with hyperthyroidism: lid lag (von Graefe sign, 1864), lid retraction (Dalrymple sign, 1849),†† and Graves ophthalmopathy. Graves ophthalmopathy afflicts exclusively patients with Graves disease, whereas lid lag and lid retraction may occur in hyperthyroidism from any etiology.

1. LID LAG

This sign describes the appearance of white sclera between the margin of the upper eyelid and corneal limbus as the patient looks downward. In von Graefe's words, "… as the cornea looks down, the upper eyelid does not follow."[64]

2. LID RETRACTION

This sign describes a peculiar staring appearance of the eyes, caused by a widened palpebral fissure. As the patient looks straight ahead, the upper eyelid is positioned abnormally high, revealing white sclera between the lid margin and superior limbus. Normally the margin of the upper eyelid rests just below the edge of the corneal limbus and covers about 1 mm of the iris.[73] Both lid lag and lid retraction are attributed in part to the sympathetic hyperactivity of hyperthyroidism, which causes excess contraction of the Müller muscle (the involuntary lid elevator whose paralysis causes the ptosis of Horner syndrome). Although the findings improve after treatment with β-blocking medications,[74] mechanisms other than sympathetic hyperactivity must contribute to the lid findings of patients with Graves disease (even those without exophthalmos or obvious ophthalmopathy; see later) because the lid findings of Graves disease may be unilateral and often persist after the patient becomes euthyroid and because the pupils of patients with lid findings are usually normal sized

** The opposite phenomenon—a "carotid bruit" emanating from the superior thyroid artery—has also been described.[70]

†† The British eye surgeon John Dalrymple (1803–1852) apparently thought so little of his sign that he never published a description of it. Writing in 1849, W. White Cooper attributed the sign to his friend Dalrymple.[71] Albrecht von Graefe (1828–1870) described his sign in 1864.[64] Ruedemann coined the term *lid lag* in 1932.[72]

(instead of the dilated pupils of sympathetic hyperactivity).[75,76] Another proposed mechanism for the lid retraction in Graves disease is an overactive levator palpebrae muscle;[77] according to this theory, the levator is overactive because its action is linked to that of the superior rectus muscle, which, in attempts to vertically align the eye, is overacting against a shortened and restricted inferior rectus muscle (see the section on Graves Ophthalmopathy).[77] Other common causes of lid retraction are contralateral ptosis, ipsilateral facial muscle weakness, previous eyelid surgery, and irritation from wearing contact lenses.[78] Ptosis causes contralateral lid retraction because attempts to elevate the weakened lid generate excessive neural signals to the motor neuron of the healthy lid, thus elevating it.[79] A simple test confirming ptosis as the cause is to occlude the eye that has ptosis, which then causes the lid retraction in the opposite eye to resolve. Facial weakness causes retraction of the ipsilateral eyelid because the lid elevators are no longer opposed by the orbicularis oculi muscle.[80]

3. GRAVES OPHTHALMOPATHY

Graves opthalmopathy is a constellation of findings, apparent in 25% to 50% of patients with Graves disease, that results from edema and lymphocytic infiltration of orbital fat, connective tissue, and eye muscles.[81,82] Characteristic physical findings are lid edema, limitation of eye movements, conjunctival chemosis and injection, and exophthalmos (as measured with an exophthalmometer). Clinicians should suspect Graves ophthalmopathy when patients complain of gritty sensation in the eyes, tearing, eye discomfort, or diplopia. The orbital swelling of Graves ophthalmopathy may threaten the optic nerve and vision. The bedside findings best predicting incipient optic neuropathy are lid edema and limitation of eye movements—not, surprisingly, the degree of proptosis (proptosis does not predict incipient optic neuropathy perhaps because intraocular pressure is relieved by the outward protrusion).[76,83]

C. CARDIOVASCULAR FINDINGS

Hyperthyroidism may cause a fast heart rate, loud snapping first heart sounds, midsystolic flow murmurs, and supraventricular arrhythmias.[84] Rare patients with severe hyperthyroidism may develop the Means-Lerman scratch,[85] a systolic rub or murmur with a prominent rough or grating character that appears near the left second intercostal space. Its pathogenesis is unknown.

D. SKIN FINDINGS[47,48]

The skin of hyperthyroid patients is warm, moist, and smooth, probably because of increased sympathetic tone to sweat glands and increased dermal blood flow. These skin findings often resolve after treatment with β-blocker medications.

Up to 4% of patients with Graves disease develop skin lesions with the confusing name **pretibial myxedema**, characterized by bilateral, asymmetric raised, firm plaques or nodules, which are pink to purple-brown in color and usually distributed over the anterior shins.[47,86]

E. NEUROMUSCULAR FINDINGS

The neuromuscular findings of hyperthyroidism are weakness and diminished exercise tolerance, tremor, and brisk ankle jerks. The diminished exercise tolerance (affecting 67% of patients) is due to an inability to increase cardiac output appropriately with exercise and to proximal muscle wasting and weakness from accelerated protein catabolism.[67,84,87] The fine tremor of hyperthyroidism occurs because of increased sympathetic tone and resolves with β-blocking medications. Brisk reflexes are noted at the bedside in only 25% of patients or less,[88] and even precise

measurements of the half-relaxation time (see the section on Hypothyroidism for definition) reveal considerable overlap between normal values (range: 230 to 420 ms) and hyperthyroid values (range: 200 to 300 ms).[49]

III. CLINICAL SIGNIFICANCE

EBM Box 25.4 presents the diagnostic accuracy of physical signs for hyperthyroidism, as applied to more than 1700 patients with suspected thyroid disease. The **Wayne index**, which combines symptoms and signs, is described fully in Table 25.2.

The findings that increase the probability of hyperthyroidism the most are lid retraction (LR = 33.2; see EBM Box 25.4), lid lag (LR = 18.6), fine finger tremor (LR = 11.5), moist and warm skin (LR = 6.8), and pulse of 90 beats/minute or more (LR = 4.5). The findings that decrease the probability of hyperthyroidism the most are normal thyroid size (LR = 0.1), pulse less than 90 beats/minute (LR = 0.2), and absence of finger tremor (LR = 0.3).

A Wayne index score of 20 or higher increases the probability of hyperthyroidism (LR = 18.2), and one less than 11 decreases the probability of hyperthyroidism

EBM BOX 25.4
*Hyperthyroidism**

Finding (Reference)	*Sensitivity (%)*	*Specificity (%)*	**Likelihood Ratio† if Finding Is**	
			Present	*Absent*
Pulse				
Pulse ≥90 beats/min[67]	80	82	**4.5**	**0.2**
Skin				
Skin moist and warm[67]	34	95	**6.8**	0.7
Thyroid				
Enlarged thyroid[67]	93	59	2.3	**0.1**
Eyes				
Eyelid retraction[67]	34	99	**33.2**	0.7
Eyelid lag[67]	19	99	**18.6**	0.8
Neurologic				
Fine finger tremor[67]	69	94	**11.5**	**0.3**
Wayne Index[89,90]				
<11 points	1-6	13-32	**0.04**	—
11-19 points	12-30	—	NS	—
≥20 points	66-88	92-99	**18.2**	—

*Diagnostic standard: for *hyperthyroidism,* high levels of protein-bound iodide (PBI) for patients evaluated in the 1960s, total thyroxine (T4) for those in the 1970s, and total T4 and thyroid-stimulating hormone (TSH) for those in the 1980s and 1990s (see footnote to EBM Box 25.3 for discussion of PBI).
†Likelihood ratio (LR) if finding present = positive LR; LR if finding absent = negative LR.
NS, Not significant.
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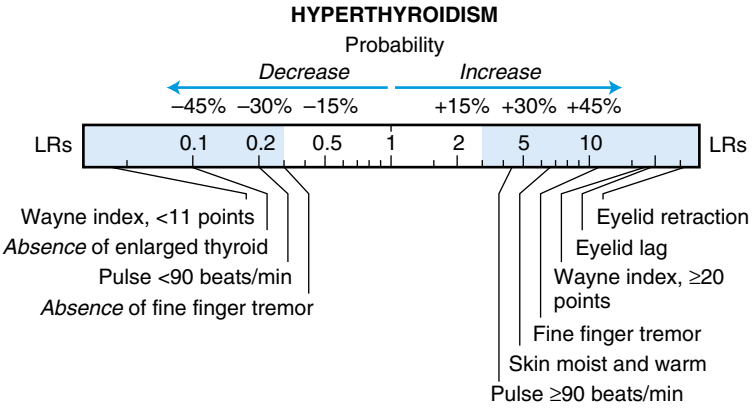

TABLE 25.2 Wayne Diagnostic Index for Hyperthyroidism*

Symptoms of Recent Onset or Increased Severity	Present	Signs	Present	Absent
Dyspnea on effort	+1	Palpable thyroid	+3	−3
Palpitations	+2	Bruit over thyroid	+2	−2
Tiredness	+2	Exophthalmos	+2	
Preference for heat (irrespective of duration)	−5	Lid retraction	+2	—
Preference for cold	+5	Lid lag	+1	—
Excessive sweating	+3	Hyperkinetic movements	+4	−2
Nervousness	+2	Fine finger tremor	+1	—
Appetite increased	+3	Hands:		
Appetite decreased	−3	Hot	+2	−2
Weight increased	−3	Moist	+1	−1
Weight decreased	+3	Casual pulse rate:		—
		Atrial fibrillation	+4	—
		<80, regular	−3	—
		80-90, regular	0	—
		>90, regular	+3	—

*Based upon reference 89.

(LR = 0.04). However, this index may be less useful in elderly patients,[91] who, as a rule, have less goiter and tachycardia than younger patients.[92-94] In one study, 36% of elderly hyperthyroid patients had scores less than 11.[69] Elderly patients also have more weight loss and atrial fibrillation than younger patients,[67,69,95,96] but the frequency of lid retraction and lid lag is the same.[67,69]

The references for this chapter can be found on www.expertconsult.com.

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